Abstract

The Children's Health Study (CHS), conducted by the University of Southern California, has reported significant associations between reduced lung function growth and exposures to nitrogen dioxide (NO_2), acid vapor, ambient particles less than 2.5 microns in diameter (PM2.5), and elemental carbon. The primary objective of this study was to use an animal model to test the hypothesis that chronic PM2.5 exposure during the period of rapid lung growth and development can lead to reduced growth in pulmonary function that is related to oxidative stress and tissue injury. We studied changes in the development of the mouse lung and lung function during chronic exposure to concentrated ambient PM2.5 using a mouse model. The mice were exposed from 3 weeks to 11 weeks of age, *i.e.* after weaning to the point where the rate of lung growth is slowed. The study also evaluated whether observed deficits in lung function persisted for up to two weeks after exposure was terminated. Mice that were exposed to concentrated ambient fine particles (CAPs) for eight weeks had reduced pulmonary function, measured as increased respiratory resistance, that persisted for up to 2 weeks after the termination of exposure. We have preserved tissue, blood, and bronchoalveolar lavage fluid samples for later analyses to investigate the relationship between pulmonary function deficits and alterations in lung structure, biochemical mediators of oxidative stress and inflammation, as well as alteration in gene expression that might be associated with lung development. We also examined the associations between particle chemical composition, particle physical characteristics and particle concentrations and observed changes in pulmonary function. There were two sets of exposures; the first exposures were performed at 'high' concentration (PM2.5, 243 $\mu g/m^3$; number concentration, 93,000 particles/cc) and the second exposures were at 'low' concentration, (PM2.5 56 $\mu g/m^3$; particle number 83,000 particles/cc). Both studies produced significant increases in resistance. Particle mass concentrations in the low study were nearly $1/5^{th}$ that in the high study, however the particle number concentrations

were nearly the same, suggesting that high concentrations of ultrafine particles were present during both sets of exposures. There were methodological differences between the two sets of exposures; however the results suggest that the ultrafine components of PM2.5 may be more strongly associated with the observed decreases in resistance in the PM-exposed developing lung than are larger-sized particle components.

Executive Summary

Background

The Children's Health Study (CHS), which was conducted by the University of Southern California for the ARB, has reported that NO_2, acid vapor, fine ambient particles and elemental carbon exposures during the period of lung growth and development in Southern California children were associated with impaired lung function growth, increased school absences, and exacerbated asthma (Kunzli et al. 2003). An earlier study by Frischer and colleagues had shown that long term exposure to ambient ozone (O_3) was associated with reduced pulmonary function growth (Frischer et al. 1999), however O_3 was not associated with pulmonary function growth deficits in the CHS (Gauderman et al. 2004a). In reviewing the CHS data, Tager suggested that the decrease in some measures of lung function growth might also have been associated with summertime levels of SO_2, NO_2 and PM10 (Tager 1999).

Specific Aims

This study had 5 specific aims:

1. Examine effects of eight week exposure to a high concentration of concentrated PM2.5 on the development of lung function and capacity in mice exposed from the time that they are weaned through 11 weeks of age (adulthood).
2. Examine the role of oxidative stress in PM-induced lung injury and pulmonary function decrements in Nrf2-/- mice.